

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Jon A. Wolff and**)
Vladimir G. Budker)

Serial No.: **09/707,117**)

Filed: **November 6, 2000**)

Group Art Unit: **1632**)

For: Intravascular Delivery of Nucleic Acid

RESPONSE TO COMMUNICATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is a response to the Communication dated September 26, 2002. Please attach this response as a supplement to the prior filed Amendment.

Support for the prior filed amendments found in the disclosure of the patent:

Teachings with respect to delivery of polynucleotide to skeletal muscle are found in the specification as follows:

Page 3, lines 4 and 5 of the specification states: "The parenchymal cell may consist of a muscle cell, such as a limb (leg or arm) muscle cell."

Page 10, lines 15-22 of the specification states: "In striated muscle, the parenchymal cells include myoblasts, satellite cells, myotubules, and myofibers. ... In one preferred embodiment striated muscle such as skeletal muscle or cardiac muscle is targeted by injecting the polynucleotide into the blood vessel supplying the tissue. In skeletal muscle an artery is the delivery vessel...."

Further support of the claimed invention providing delivery of polynucleotides to skeletal muscle is found in the examples, specifically: example 3 on page 25, example 7 on page 30, examples 8 and 9 on page 31 and example 10 on page 32.

Teachings with respect to applying pressure to the mammal's limb epidermis to impede blood flow are found in the specification as follows:

Page 5, lines 13-24 of the specification states: "The term cuff means a device for impeding blood flow through mammalian internal blood vessels. However, for purposes of the claims, cuff refers specifically to a device applied exterior to the mammal's skin and touches the skin in a non-invasive manner. ... The vessel walls are forced to constrict in an

area underneath the cuff in amount sufficient to impede blood from flowing at a normal rate. ... One example of a cuff is a sphygmomanometer which is normally used to measure pressure. In a preferred embodiment of this specification, the sphygmomanometer is used to apply pressure to mammalian skin, around a limb, for the purpose of increasing vessel permeability. Another example is a tourniquet.

In example 1 on page 23, the use of a sphygmomanometer cuff surrounding the arm or leg proximal to the injection site to facilitate delivery of polynucleotides to muscle cells in primates is described. Similarly, the use of a tourniquet to facilitate delivery of polynucleotides to muscle cells in rats is described.

The data in examples 7 and 10 illustrate the increased delivery of polynucleotides to muscle tissue when blood flow occlusion is used during the process.

Teachings with respect to transient and continuous immunosuppression are found in the specification as follows:

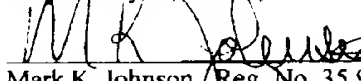
Page 3, lines 26-33 of the specification states: "In a preferred embodiment it may be preferential to immunosuppress the host receiving the nucleic acid. Immunosuppression can be long term or for a short duration.... This can be accomplished by treatment with (combinations of) immunosuppressive drugs like cyclosporin A, ProGraf (FK506), corticosteroids, deoxyspergualin, and dexamethasone. Other methods include blocking of immune cell activation pathways

The use of immunosuppressive drugs to enhance or prolong expression of delivered polynucleotides is found in example 5 on page 28 and in examples 8 and 9 on page 31.

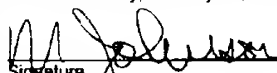
Teachings with respect to the delivery of polynucleotides resulting in expression at detectable levels are found in the specification in examples 3 and 5-10. In each of these examples, expression of delivered polynucleotide encoded genes is measured. These genes include the marker genes luciferase, β -galactosidase and SEAP as well as a therapeutic gene human factor IX.

Teachings with respect to maintaining limb function are found in the specification in examples 3 and 4. Example 3 states: "All seven monkeys tolerated the procedure well and had full function of their arms, hands, legs and feet following the procedure. In particular, this indicates lack of damage to the radial nerve.... Swelling in the target limbs, a putative correlate of successful gene transfer, was noted afterwards but completely subsided by the next day. It is noted in example 4 that the muscle tissue was well preserved and did not show any sign of pathology.

Respectfully submitted,


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GROUP 1600

PTO/SB/21 (08-00)

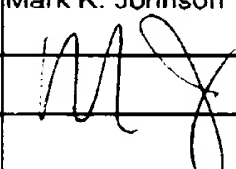
Applicant's use through 10/31/2002. OMB 0651-0031

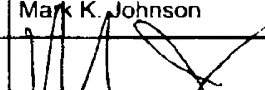
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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| | | |
|--|-----------------------------|----------------|
| TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i> | Application Number | 09/707,117 |
| | Filing Date | 11/06/2000 |
| | First Named Inventor | Jon A. Wolff |
| | Group Art Unit | 1632 |
| | Examiner Name | Michael Wilson |
| Total Number of Pages in This Submission | | 6 |
| Attorney Docket Number | | 18.02 |

| ENCLOSURES (check all that apply) | | | | |
|--|---|--|---------|--|
| <input checked="" type="checkbox"/> Fee Transmittal Form <input checked="" type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment / Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/ Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53 | <input type="checkbox"/> Assignment Papers (for an Application) <input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ | <input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input type="checkbox"/> Other Enclosure(s) (please identify below): | | |
| <table border="1" style="width: 100%;"> <tr> <td style="width: 100px; height: 40px; vertical-align: top;">Remarks</td> <td></td> </tr> </table> | | | Remarks | |
| Remarks | | | | |

| SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT | |
|--|---|
| Firm or Individual name | Mark K. Johnson |
| Signature |  |
| Date | 01/03/2003 |

| CERTIFICATE OF MAILING | | | |
|---|---|------|------------|
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| | | | 01/03/2003 |
| Typed or printed name | Mark K. Johnson | | |
| Signature |  | Date | 01/03/2003 |

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PTO/SB/17 (10-01)

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**FEE TRANSMITTAL
for FY 2003**

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT (\$) **460.00****Complete if Known**

| | |
|----------------------|----------------|
| Application Number | 09/707,117 |
| Filing Date | 11/06/2000 |
| First Named Inventor | Jon Wolff |
| Examiner Name | Michael Wilson |
| Group Art Unit | 1633 |
| Attorney Docket No. | Mirus.018.02 |

METHOD OF PAYMENT

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:
- Deposit Account Number
- Deposit Account Name
- ☐ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17
- ☐ Applicant claims small entity status. See 37 CFR 1.27
2. ☐ **Payment Enclosed:**
- ☐ Check ☒ Credit card ☐ Money Order ☐ Other

FEE CALCULATION**1. BASIC FILING FEE**

| Large Entity | | Small Entity | | Fee Description | Fee Paid |
|--------------|----------|--------------|----------|------------------------|----------|
| Fee Code | Fee (\$) | Fee Code | Fee (\$) | | |
| 101 | 740 | 201 | 370 | Utility filing fee | |
| 106 | 330 | 206 | 185 | Design filing fee | |
| 107 | 510 | 207 | 255 | Plant filing fee | |
| 108 | 740 | 208 | 370 | Reissue filing fee | |
| 114 | 160 | 214 | 80 | Provisional filing fee | |

SUBTOTAL (1) (\$) **2. EXTRA CLAIM FEES**

Total Claims - 20** = X =

Independent Claims - 3** = X =

Multiple Dependent =

| Large Entity | | Small Entity | | Fee Description |
|--------------|----------|--------------|----------|--|
| Fee Code | Fee (\$) | Fee Code | Fee (\$) | |
| 103 | 18 | 203 | 9 | Claims in excess of 20 |
| 102 | 84 | 202 | 42 | Independent claims in excess of 3 |
| 104 | 280 | 204 | 140 | Multiple dependent claim, if not paid |
| 109 | 84 | 209 | 42 | ** Reissue independent claims over original patent |
| 110 | 18 | 210 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) (\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

| Large Entity | | Small Entity | | Fee Description | Fee Paid |
|--------------|----------|--------------|----------|--|----------|
| Fee Code | Fee (\$) | Fee Code | Fee (\$) | | |
| 105 | 130 | 205 | 65 | Surcharge - late filing fee or oath | |
| 127 | 50 | 227 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 139 | 130 | 139 | 130 | Non-English specification | |
| 147 | 2,520 | 147 | 2,520 | For filing a request for ex parte reexamination | |
| 112 | 920* | 112 | 920* | Requesting publication of SIR prior to Examiner action | |
| 113 | 1,840* | 113 | 1,840* | Requesting publication of SIR after Examiner action | |
| 115 | 110 | 215 | 55 | Extension for reply within first month | |
| 116 | 400 | 216 | 200 | Extension for reply within second month | |
| 117 | 920 | 217 | 460 | Extension for reply within third month | 460.00 |
| 118 | 1,440 | 218 | 720 | Extension for reply within fourth month | |
| 128 | 1,960 | 228 | 980 | Extension for reply within fifth month | |
| 119 | 320 | 219 | 160 | Notice of Appeal | |
| 120 | 320 | 220 | 160 | Filing a brief in support of an appeal | |
| 121 | 280 | 221 | 140 | Request for oral hearing | |
| 138 | 1,510 | 138 | 1,510 | Petition to institute a public use proceeding | |
| 140 | 110 | 240 | 55 | Petition to revive - unavoidable | |
| 141 | 1,280 | 241 | 640 | Petition to revive - unintentional | |
| 142 | 1,280 | 242 | 640 | Utility issue fee (or reissue) | |
| 143 | 460 | 243 | 230 | Design issue fee | |
| 144 | 620 | 244 | 310 | Plant issue fee | |
| 122 | 130 | 122 | 130 | Petitions to the Commissioner | |
| 123 | 50 | 123 | 50 | Processing fee under 37 CFR 1.17(a) | |
| 126 | 180 | 126 | 180 | Submission of Information Disclosure Stmt | |
| 581 | 40 | 581 | 40 | Recording each patent assignment per property (times number of properties) | |
| 146 | 740 | 246 | 370 | Filing a submission after final rejection (37 CFR § 1.129(a)) | |
| 149 | 740 | 249 | 370 | For each additional invention to be examined (37 CFR § 1.129(b)) | |
| 179 | 740 | 279 | 370 | Request for Continued Examination (RCE) | |
| 189 | 900 | 189 | 900 | Request for expedited examination of a design application | |

Other fee (specify)
SUBTOTAL (3) (\$) **460.00****SUBMITTED BY**

Complete (if applicable)

| | | | | | |
|-------------------|---|-----------------------------------|------------|-----------|--------------|
| Name (Print/Type) | Mark K. Johnson | Registration No. (Attorney/Agent) | 35,909 | Telephone | 262.821.5690 |
| Signature |  | Date | 01/03/2003 | | |

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